

## How reliable is the history of chickenpox? Varicella serology among children up to 14 years of age

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**Objectives:** The aim of this study was to assess the seroprevalence of antibodies to varicella-zoster virus (VZV) in children of northern Greece and to estimate the reliability of varicella history.

**Methods:** A serosurvey of 632 children, aged 13 months to 14 years (median 5.2 years), was conducted between April 1999 and July 2001. Serum samples were tested by enzyme-linked immunosorbent assay (ELISA) for IgG antibodies to VZV (IgG Genzyme Virotech GmbH). A history of varicella in these children was obtained from the parents of all these patients. Also, a check of state health cards of the patients was done.

**Results:** Two hundred and forty-eight (39%) of the children were seropositive for VZV. Two hundred and thirty (36%) of the 632 children claimed to have had previous varicella infection; 87.8% were seropositive, and 12.2% lacked antibodies to VZV. One hundred and seven of the 230 children with a history of varicella had the information about the disease confirmed, as it was reported on their state health card by a pediatrician; 10.2% were seronegative for VZV. Absence of history of varicella was reported in 402 (63.6%) of the 632 children; 88.6% of those were seronegative, and 11.4% were seropositive. The percentage of incorrect negative history ranged from 6% (13–60 months of age) to 48% (120–168 months of age).

**Conclusions:** A large proportion of the study group (61%), mainly below 7 years of age, is susceptible to varicella. The positive predictive value of a history of varicella is 87.8%, whereas the negative predictive value of a negative history is 11.4%, which means that there is an 88.6% probability of a negative history being correct. Varicella serology may be reasonable prior to vaccination in children >10 years old with a negative chickenpox history. However, if one excludes cost considerations, it is also reasonable to vaccinate all children, irrespective of serostatus.

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### INTRODUCTION

Varicella is due to primary infection with varicella-zoster virus (VZV) and is manifested with a characteristic vesicular exanthem. A history of such exanthem is usually strong evidence of varicella infection.<sup>1,2</sup> However, subclinical infection is well described, mainly in healthy adults and less frequently in children.<sup>3</sup> The vaccine used against varicella is licensed in some countries and will soon be licensed in many others. It is generally believed that vaccination will have a significant effect against the disease.<sup>4</sup> However, pediatricians have to perform a vaccination based on parent history for varicella or on serology for varicella. The cost of each decision is different, and the cost of serology varies according to the country. A third alternative is to give the vaccine to all children, irrespective of history or serostatus. This policy has no adverse effects in already immune children; there is only the cost of an additional vaccination.

The aim of this study was to assess the seroprevalence of antibodies to VZV in children of northern Greece, and to estimate the reliability of varicella history. This will enable the pediatrician to be better informed and will improve clinical policy.

### MATERIALS AND METHODS

During the period April 1999 to July 2001, a serosurvey for antibodies against VZV in children hospitalized in our department was conducted. Children admitted for varicella were excluded from the study.

During the study period, serum samples were taken from 632 children (study group), aged 13–168 months (mean age 62.4 months). All serum samples were taken with parental consent. Blood was obtained for other investigations, so the venepuncture was not done solely for the purpose of this study. Two hundred and forty of these patients (53.8%) were male.

For semiquantitative determination of IgG antibodies to VZV in serum samples, an enzyme-linked immunoassay (ELISA Genzyme Virotech GmbH, Russelsheim, Germany) was used. The antibody detected in the serum forms an immune complex with the antigen coated on the test strips. The enzyme conjugate attaches to this complex. After addition of the substrate buffer (tetramethylbenzidine (TMB)), a blue dye is produced by

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the bound enzyme (peroxidase). The color changes to yellow when the stopping solution is added. The intensity of the color is proportional to the serum concentration of antibodies. If the measured values of the samples are 10% above the cutoff value, the samples are positive, and if they are 10% below the cutoff value, the samples are negative. The cutoff value given by Virotech has been compared with the WHO Serum W1044 and corresponds to 250 mIU/mL. The specificity and sensitivity of the ELISA are 96% and 91% respectively.

A history of varicella in these children was obtained from the parents. The interview was done before the varicella serology results were made available. Parents were asked about prior varicella exposure and disease, and were given a full description of the clinical manifestations of varicella. We considered only answers that definitely supported past chickenpox as being indicative of a positive history. The educational status of the parents was average for 80%, high for 10%, and elementary for 10%. Elementary educational status is defined as grade school, average status as high school and lyceum, and high status as university and technical college.

All the state health cards of the study group children were checked for past varicella diseases. This is an official card on which is recorded every examination of the children, their vaccinations, diseases, their growth, etc. We considered as positive only reports with a signature and the name of the pediatrician.

Infants <12 months old were excluded from the study, first because parents remember the history of their child during this small period of time more easily, second because the varicella vaccine is licensed for ages above 12 months, and third because residual maternal antibodies exist.

Our department is a referral center for varicella in an area of about 3 000 000 people, and it is considered that the sample is representative of the Greek population.

## RESULTS

Two hundred and forty-eight (39%) of the children were seropositive for VZV antibodies. Two hundred and thirty (36.4%) of the 632 patients claimed to have had previous varicella; 87.8% of those were seropositive, while 12.2% lacked antibodies to VZV (Table 1). The percentage of the wrong positive history for varicella (no antibodies) was 13.8% (17/123 varied according to the age of the patients: 13–60 months, 6/36 (16.7%);

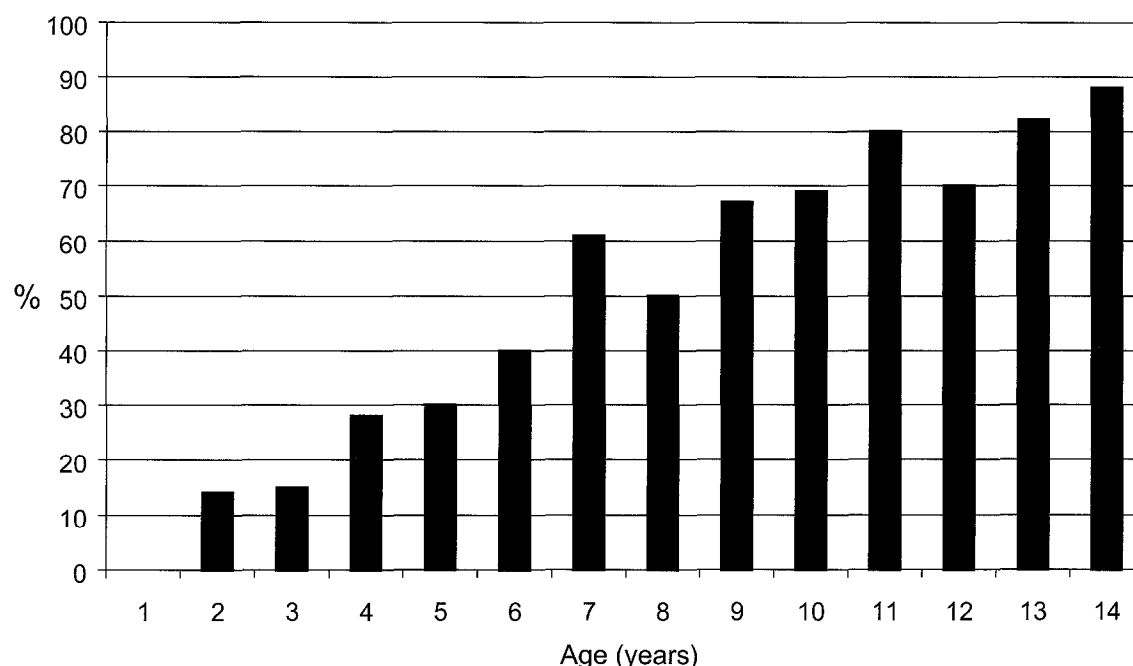
61–120 months, 7/57 (12.2%); 121–168 months, 4/30 (13.3%)). One hundred and seven of the 230 children with positive varicella history had the disease confirmed, as it was reported in their state health card by a pediatrician; 10.2% of them were seronegative for VZV. The percentage of wrong diagnosis by pediatricians in cases of a history of varicella varied according to the age of the patients: 13–60 months, 4/40 (10%); 61–120 months, 4/51 (7.8%); 121–168 months, 3/16 (18.8%). No history of varicella was reported for 402 (63.6%) of the 632 children; 88.6% of them were seronegative, and 11.4% were seropositive. Again, the percentage of incorrect negative history varied according to age: 13–60 months, 17/282 (6.0%); 61–120 months, 17/95 (17.9%); 121–168 months, 12/25 (48%). The distribution of antibodies according to age showed that the proportion of sera that were positive increased with age (Figure 1). The total results according to age are shown in Table 2.

## COMMENTS

Varicella remains a common, highly infectious and sometimes severe disease of childhood. The annual incidence of varicella is high in Greece as well as in many other parts of the world,<sup>1,3,5,6</sup> leading to many physician visits and hospitalizations, and much loss of employment time. Chickenpox is manifested by a characteristic vesicular rash, on which the diagnosis and the consequent clinical history are based.<sup>1</sup> A history of previous varicella infection is usually an accurate predictor of varicella immunity.<sup>1,2,7</sup> However, history alone may not be reliable under certain circumstances. Subclinical infection has been reported in adults, as well as in children.<sup>3,8</sup> The pediatrician must have a clear picture of the epidemiology of varicella in order to provide a vaccine based on history only or on serology. The latter will be cost-effective only if serology is cheaper than the vaccine. The alternative of giving the vaccine to all children irrespective of history or serostatus is a good option if cost is not a factor. It is much better to do an additional vaccination (with all the known benefits of vaccination) than to lose a vaccination because parents will not be back again, or will refuse to give a blood sample for serology to confirm varicella. The analysis of our data shows that 10.2% of children with a positive clinical history of VZV infection, confirmed by their pediatrician, had no VZV antibodies. The corresponding percentage in children with varicella history confirmed by their parents was 12.2%. These percentages are higher than those in other studies.<sup>9</sup> However, the method of measuring antibodies that we used is a sensitive and reliable one, especially for epidemiologic purposes, and is comparable with other methods (fluorescent antibodies—membrane antigen (FAMA etc.)).<sup>8,10,11</sup> Finally, among children with a negative history of chickenpox, varicella seroprevalence was 11.4%, ranging from 6% (13–60 months of age) to 48% (120–168 months of age), a figure smaller than in

**Table 1.** Varicella antibody profile of 632 children

Varicella history	No. of children	Positive antibodies		Predictive value	
		No.	(%)	Positive	Negative
Positive	230	202	87.8	87.8	12.2
Negative	402	46	11.4	88.6	11.4



**Figure 1.** VZV antibody distribution (%) according to the age of children.

**Table 2.** Rate of anti-VZV antibodies and varicella history in 632 children according to age

Age (months)	No. of children	Positive varicella history		Negative varicella history		Positive varicella history by a pediatrician	
		No. of children	(-) VZV antibodies	No. of children	(+) VZV antibodies	No. of children	(-) VZV antibodies
13–24	119	12	2	105	3	2	0
25–36	106	9	1	88	4	9	1
37–48	62	3	1	44	3	15	1
49–60	71	12	2	45	7	14	2
61–72	67	12	1	39	8	16	1
73–84	27	6	1	13	1	8	0
85–96	46	16	4	23	3	7	0
97–108	35	13	0	11	2	11	1
109–120	28	10	1	9	3	9	2
121–132	25	16	1	5	0	4	1
133–144	21	5	1	12	6	4	1
145–156	11	5	1	4	3	2	0
157–168	14	4	1	4	3	6	1
Total	632	123	17	402	46	107	11

other studies.<sup>12</sup> Serology would be reasonable in patients >10 years old without a history of varicella.

In our study, the rate of susceptibility to varicella in children is high. This rate is higher than in other studies.<sup>9,13,14</sup> Therefore, the widespread use of varicella vaccine should have a significant impact on the epidemiology of varicella-zoster infections.

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